REMARKS

Specification

By the present amendment, Applicants have deleted the priority claim as entered with the amendment filed February 2, 2005, and have inserted in its place, paragraph [0001.1]. Applicants hereby cancel their claim to the priority of application No. 09/606,909, filed June 29, 2000. Upon entry of the amendment, Applicants submit that the priority claim will recite that the instant application is a continuation-in-part of U.S. application no. 09/843,746, filed June 29, 2001.

Claims

By the present amendment, claims 36 and 44 have been amended to correct typographical errors. No new matter has been added.

Claims 1-34 and 36-73 are pending, with claims 1-30 and 53-66 standing withdrawn.

I. THE CLAIMS ARE PATENTABLE OVER TO GROSS. IN VIEW OF PURI OR D'ANTONIO OR D'ANTONIO, GANDERTON, OR AUTRET

Claims 33-52 and 67-73 are rejected over U.S. Patent No. 5,848,991 to Gross *et al.* (Gross) in view of Puri *et al.*, 2000, *Vaccine,* 18: 2600-12 (Puri) or U.S. Patent No. 6,056,716 to D'Antonio *et al.* (D'Antonio). According to the Examiner, Puri and D'Antonio suggest that intradermal injections give much greater C_{max} and AUC values.[1] The Examiner reasons that it would have been obvious to use the teachings of Gross in order to effectively treat patients and save drug costs. For the following reasons, Applicants respectfully disagree.

Claims 31 and 67 recite methods comprising delivering a bolus of the substance intradermally via a needle inserted into the patient's skin so that the needle penetrates the intradermal compartment. The claims specify that the needle's outlet depth and exposed height of the outlet are located within the intradermal compartment, wherein the outlet has an exposed height of about 0 to 1 mm, so that the substance is delivered into the intradermal compartment and distributed systemically exhibiting a higher C_{max} and a shorter T_{max} of the substance, by comparison with subcutaneous administration of the substance at an identical dose and rate of delivery.

[1] Applicants note that the claims 31 and 67 recite exhibiting a higher C_{max} and shorter T_{max}, and not a higher AUC as the Examiner contends.

The References Fail to Teach or Suggest the Claimed Needle Configuration

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); and M.P.E.P. § 2143.03.

Here, Gross does not describe the insertion of a needle so that *both* its outlet depth and exposed height of the outlet are located within the intradermal compartment of the subject's skin as specified in claims 31 and 67. Further, Gross does not describe a needle having an outlet with an exposed height of about 0 to 1 mm. These elements of the claims are not taught or suggested by Gross. Instead, Gross proposes methods and devices that *non-selectively* administer drugs below the epidermis, *i.e.*, to the interface between the epidermis and the dermis, or to the interior of the dermis or subcutaneously (*see*, Gross at col. 3, *ll.* 38-45).

Indeed, practice of the claimed method of intradermal delivery has a very different outcome as compared to delivery in accordance with Gross as demonstrated by the Third Declaration under § 1.132 of Dr. Ronald J. Pettis ("Declaration") submitted June 18, 2007 in copending Appl. Serial No. 09/606,909, filed June 29, 2000 (Exhibit 1). The Declaration demonstrates that delivery in accordance with the claimed configuration has a dramatic effect on the results obtained when compared to the results reported by Gross. Namely, administration in accordance with the claimed configuration dramatically affects the resulting pharmacodynamic profile, including both the rate and magnitude of the drop in blood glucose concentration as compared to Gross. *See*, Declaration.

As reported in Example 1 of Gross, when insulin was administered "intradermally" to rabbits, the rabbits' glucose levels dropped, and rose again when insulin administration ceased. However, rabbits receiving insulin in accordance with the claimed method demonstrated a much more precipitous drop in blood glucose concentrations. *See*, Declaration at ¶ 15 and Exhibits B, C, D, and E. In fact, as a result of intradermal administration of insulin in accordance via the claimed method at 100 IU/mL, the blood glucose concentrations of the test animals dropped to levels which could not be reversed by ceasing administration of insulin, nor by intervening through administration of glucose to the hypoglycemic test animals. This result indicates that there apparently was a high maximum plasma concentration and bioavailability of insulin when it was administered via the claimed method; hence the same hypoglycemic shock experienced by the test animals, as opposed to the result obtained by the methodology described in Gross, where the animals easily

recovered once insulin administration ceased. Had Gross been practicing intradermal delivery as claimed in the instant application, the same result would have been observed; it was not. *See*, Declaration at ¶ 8.

One possible explanation for the differences in the observed pharmacodynamic response is that Gross fails to define the intradermal compartment, but merely describes delivery below the epidermal layer of the skin. Gross is devoid of any teaching relating to the configuration of the needle required to prevent leakage of the drug substance outside the intradermal space. It is the Applicants' disclosure, not Gross, which teaches the importance of not only the length of the needle, but the relative exposed height of the needle outlet (*e.g.*, the bevel) that could be used to successfully target the intradermal compartment. (*See*, specification at p. 18, *l.* 22-p. 19, *l.* 28). Unless the skin seals around the needle, the drug substance will effuse out of the skin due to backpressure exerted by the skin itself, or the pressure built up from the accumulating fluid. The Applicants' specification sets forth principles and parameters relating to length of the needle and configuration of its outlet to prevent unwanted leakage. The Applicants' teachings also address mechanisms that can be used to provide adequate pressure so that the drug is efficiently and consistently delivered to the intradermal compartment of human skin where it is readily absorbed and systemically distributed. (For proper needle length and outlet configuration, *see*, instant specification at p. 18, *l.* 22-p. 19, *l.* 12; for proper pressure requirements to achieve intradermal delivery *see*, instant specification at p. 19, *ll.* 13-28). In particular, the specification describes the use of microneedles that have *both* a length sufficient to penetrate the intradermal space *and* an *outlet depth within the penetration space* to allow the skin to seal around the needle to prevent effusion of the substance onto the surface of the skin due to backpressure (*see*, specification at p. 18, *l.* 23-p. 19, *l.* 12). Gross neither appreciates nor addresses the significance of these parameters for practicing the claimed method.

Puri, D'Antonio, Ganderton, and Autret do not remedy these deficiencies as they fail to teach or suggest the claimed needle configuration (a needle outlet with an exposed height of about 0 to 1 mm) and the claimed positioning of the needle outlet within the skin.

The References Fail to Teach or Suggest the Claimed Pharmacokinetic Profile

In addition, not only is Gross silent as to the claimed pharmacokinetic profile, practicing Gross does not inevitably result in the claimed profile. As set forth in the Supplemental Declaration by Dr. Ronald J. Pettis under 37 § 1.132, submitted with the

Amendment filed August 9, 2006, mere injection of a drug in to the intradermal compartment does not inevitably result in an enhanced PK profile as compared to subcutaneous administration.

Contrary to the Examiner's position, Puri and D'Antonio do not teach or suggest a higher C_{max} and shorter T_{max} as claims 31 and 67 specify. Puri and D'Antonio relate to vaccine delivery. The efficacy of a vaccine is measured by the ability of the body to mount an antibody response to the vaccine. Methods of assaying potency of immunogenic compositions such as vaccines include serologic testing such as measurement of antibody titers induced against the particular antigen. For example in Puri, an ELISA assay was developed to quantify antibody levels (not injected vaccine) in the sera of immunized mice. Similarly, D'Antonio makes reference, not to a PK profile, but rather to a more rapid and effective pickup by the immune system (*see*, col. 29, *ll.* 22-26).

The Examiner has improperly attributed parameters and properties of the drug delivery art to the vaccine art. Pharmacokinetic studies are meaningless in the vaccine art as practitioners in this field do not gauge the potency of a vaccine by its ability to be circulated systemically. Thus, Puri and D'Antonio do not describe, nor do they suggest that their administration methods achieve a higher C_{max} and shorter T_{max} of the substance as compared to subcutaneous administration of the substance at an identical dose and rate of delivery as required by the claims.

The Examiner relies on Ganderton for the teaching of injecting a substance through multiple microneedles, and alleges that modifying the combination of Gross, Puri, and D'Antonio by using an apparatus having multiple needles would have been obvious for a person of ordinary skill in the art. However, as Applicants have set forth above, the combination of Gross, Puri, and D'Antonio fails to satisfy the legal standard for an obviousness rejection. Absent a teaching or suggestion in Ganderton that a higher C_{max} and shorter T_{max} of the administered substance is achieved by comparison with subcutaneous administration of the substance at an identical dose and rate of delivery, Ganderton does not cure the deficiencies of the Examiner's combination.

In addition, the Examiner relies on Autret for the disclosure that intradermal injection of a hormone results in a pharmacokinetic profile similar to subcutaneous delivery, and alleges that modifying the combination of Gross, Puri, and D'Antonio by infusing hormones would have been obvious for a person of ordinary skill in the art. However, as Applicants have set forth above, the combination of Gross, Puri, and D'Antonio fails to satisfy the legal

standard for an obviousness rejection. Absent a teaching or suggestion in Ganderton that intradermal administration achieves a higher C_{max} and shorter T_{max} of the substance in comparison with subcutaneous administration of the substance at an identical dose and rate of delivery, Ganderton does not cure the deficiencies of the Examiner's combination. Indeed, Autret reports that the plasma levels of calcitonin resulting from intradermal and subcutaneous administration are *not different* (*see*, Autret, Summary at p. 5), and not a higher C_{max} and shorter T_{max} as claims 31 and 67 require.

In sum, none of the references taken alone or in combination describe or suggest administration via a needle having the claimed configuration and placement in the intradermal compartment. The references taken alone or in combination are equally silent as to the improved pharmacokinetic profile – a higher C_{max} and shorter T_{max} of the substance when delivered intradermally. Accordingly, Applicants request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

II. THE CLAIMS ARE PATENTABLE OVER GROSS IN VIEW OF PURI, OR D'ANTONIO, GANDERTON, OR AUTRET IN FURTHER VIEW OF ERIKSSON, PALASIS, PRAUSNITZ, ROSENBERG, LASTOVICH, HJERTMAN, CARSON, KLING, SON OR RIETHMULLER.

Claims 33-52 and 67-73 are rejected over Gross in view of Puri, or D'Antonio , Ganderton, or Autret, in further view of Eriksson (U.S. Patent No. 6,525,030), Palasis (U.S. Patent No. 6,319,230), Prausnitz (U.S. Patent No. 6,503,231), Rosenberg (U.S. Patent No. 6,623,457), Lastovich (U.S. Patent No. 6,808,506), Hjertman (U.S. Patent No. 5,873,856), Carson (U.S. Patent No. 5,241,969), Kling (U.S. Patent No. 4,373,526), Son (U.S. Patent No. 2,559,474), or Riethmuller (U.S. Patent No. 1,274,081). The Examiner's rejection over Gross in view of Puri, and the Examiner's rejection over D'Antonio , Ganderton, or Autret are set forth above.

As Applicants have set forth above, the combination of Gross, Puri, and D'Antonio in further view of Ganderton and Autret fails to satisfy the legal standard for an obviousness rejection. The combination fails to teach or suggest the claimed needle configuration and positioning of the needle outlet within the skin; and further the combination fails to teach or suggest the improved pharmacokinetic profile – a higher C_{max} and shorter T_{max} of the substance when delivered intradermally. None of the other cited references Eriksson, Palasis, Prausnitz, Hjertman, Carson, Kling, Son, or Riethmuller remedy these deficiencies.

Furthermore, Applicants submit that Lastovich does not constitute prior art for purposes of 35 U.S.C. § 103. Lastovich published November 27, 2003 as U.S. Application Publication No. 2003/0220610. Lastovich claims the priority of several provisional applications, the earliest of which is February 4, 2002. The present application was filed December 28, 2001 and claims the priority of U.S. application No. 09/893,746, filed June 29, 2001. Thus, the instant application's filing date precedes both the filing and publication dates for Lastovich, and therefore Lastovich is not prior art.

Applicants further submit that Rosenberg cannot qualify as prior art to the instant invention under 35 U.S.C. § 103. Rosenberg published September 23, 2003, after the instant application's filing date of December 29, 2001 and priority date of June 29, 2001. The subject matter in Rosenberg was at the time the instant invention was made, owned by the same person or subject to an obligation of assignment to the same party, Becton Dickinson and Company, as indicated by the named assignee on the face of Rosenberg and the recorded assignment in the present application (*see*, Reel/Frame: 013947/0640). Therefore, under 35 U.S.C. § 103(c), Rosenberg cannot preclude patentability of the claimed invention.

Accordingly, for the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Entry of the foregoing amendments and remarks into the record of the above-identified application is respectfully requested. Applicants submit that the amendments and remarks made herein now place the application in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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Enclosures